Incidence Rate of Kaposi Sarcoma in HIV-Infected Patients on Antiretroviral Therapy in Southern Africa: A Prospective Multicohort Study

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Background: The risk of Kaposi sarcoma (KS) among HIV-infected persons on antiretroviral therapy (ART) is not well defined in resource-limited settings. We studied KS incidence rates and associated risk factors in children and adults on ART in Southern Africa.

Methods: We included patient data of 6 ART programs in Botswana, South Africa, Zambia, and Zimbabwe. We estimated KS incidence rates in patients on ART measuring time from 30 days after ART initiation to KS diagnosis, last follow-up visit, or death. We assessed risk factors (age, sex, calendar year, WHO stage, tuberculosis, and CD4 counts) using Cox models.

Findings: We analyzed data from 173,245 patients (61% female, 8% children aged <16 years) who started ART between 2004 and 2010. Five hundred and sixty-four incident cases were diagnosed during 343,927 person-years (pys). The overall KS incidence rate was 164/100,000 pys [95% confidence interval (CI): 151 to 178]. The incidence rate was highest 30–90 days after ART initiation (413/100,000 pys; 95% CI: 342 to 497) and declined thereafter [86/100,000 pys (95% CI: 71 to 105), >2 years after ART initiation]. Male sex [adjusted hazard ratio (HR): 1.34; 95% CI: 1.12 to 1.61], low current CD4 counts (≥500 versus <50 cells/μL, adjusted HR: 0.36; 95% CI: 0.23 to 0.55), and age (5–9 years versus 30–39 years, adjusted HR: 0.20; 95% CI: 0.05 to 0.79) were relevant risk factors for developing KS.

Interpretation: Despite ART, KS risk in HIV-infected persons in Southern Africa remains high. Early HIV testing and maintaining high CD4 counts is needed to further reduce KS-related morbidity and mortality.

Key Words: Kaposi sarcoma, incidence rate, HIV, AIDS, antiretroviral therapy, cohort study

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INTRODUCTION

Kaposi sarcoma (KS) is the most common cancer in HIV-infected persons in Southern Africa. KS is caused by human herpesvirus 8 (HHV-8), which is very common in Southern Africa; 35%–50% of HIV-infected persons living in this region are coinfected with HHV-8.[1,2] HIV infection is one of the main risk factors for developing KS and affects between 10%–25% of the general population in Southern African countries.[3] KS incidence rate in HIV-infected persons can be reduced by 70%–90% if the HIV infection is treated with antiretroviral therapy (ART).[4–6]

Since 2004, ART has become widely available in most Southern African countries,[7] and hopes have arisen that the KS burden would decrease. Three studies conducted in Africa found KS incidence rates between 138/100,000 and 340/100,000 person-years (pys) in patients treated with ART.[5,8,9] These estimates suggest that the risk for developing KS in patients on ART is still substantial. To effectively plan and implement measures to reduce the KS burden in Africa, more reliable information on the KS risk in patients on ART and associated risk factors is needed.

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Our goals were to estimate the incidence rate of KS in HIV-infected children and adults on ART in Southern Africa within the framework of the International epidemiological Databases to Evaluate AIDS (IeDEA) and to identify risk factors associated with KS development in these patients.

METHODS

The International Epidemiological Databases to Evaluate AIDS

IeDEA is a global research consortium established in 2005 with 7 regional networks (including 4 networks in sub-Saharan Africa) that collect clinical and epidemiological data on HIV-infected people. The African networks of IeDEA have been described in detail elsewhere.[10] The Southern African region of IeDEA-SA includes ART programs in 7 countries (Botswana, Malawi, Lesotho, Republic of South Africa, Zambia, Mozambique, and Zimbabwe). All cohorts have been approved by local ethics committees or institutional review boards, use standardized methods of data collection, and schedule follow-up visits at least once every 6 months. Data are collected on patient demographics, use of ART, CD4 cell counts, AIDS-defining events and other complications, and deaths (see www.iedea-sa.org). Cohorts transfer their data to coordinating centers at the School of Public Health and Family Medicine, University of Cape Town, South Africa, and the Institute of Social and Preventive Medicine, University of Bern, Switzerland.

Inclusion Criteria and Definitions

We included data from cohorts in IeDEA-SA, which systematically recorded KS episodes in children and adults as part of routine clinical care. We included all ART-naive HIV-1–infected patients who started treatment between 2004 and 2010 (ART had become more widely available in Southern Africa from 2004 on). Data were merged on February 28, 2011. We excluded patients who had been diagnosed with KS before or within 1 month after they began ART (considered as prevalent KS cases) and all patients who were not followed up for at least 30 days. CD4 cell count at ART initiation was defined as CD4 cell count closest to ART initiation (between 180 days before until 30 days after). We defined ART as a regimen of at least 3 antiretroviral drugs from any drug class, including protease inhibitors, nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors.

Statistical Analysis

We calculated incidence rates by dividing the number of patients who developed KS by the number of person-years at risk. We measured time from 30 days after ART initiation until the date of KS diagnosis, the last follow-up visit, or death. We used an intent-to-continue treatment approach not accounting for subsequent treatment changes, treatment interruptions, or terminations. We present KS incidence rates for the entire period of observation and for different periods after starting ART, that is, 30–90 days, >3–6 months, >6–12 months, >1–2 years, and >2 years after ART initiation. We assessed the following risk factors for developing KS: age, sex, CD4 cell counts at ART initiation, current CD4 cell counts, current or past tuberculosis (TB), and WHO clinical stages I/II versus stages III/IV. In a sensitivity analysis, we evaluated WHO clinical stages I–III versus stage IV. Risk factors for incident KS were estimated using crude and adjusted Cox proportional hazard models. The multivariable models included sex, age, calendar period, WHO clinical stage at ART initiation, and current CD4 cell counts. The selection of the included variables was not automated but based on biological and epidemiological rationale. Children below the age of 5 years were excluded from univariable and multivariable analyses that used absolute CD4 cell counts because CD4 cell percentages are recommended for that age group instead. To assess potential selection bias, we conducted 2 sensitivity analyses with varying definitions of incident KS and re-examined the impact of CD4 cell counts at the time of ART initiation on the risk for developing KS. In 1 sensitivity analysis, we included all KS cases diagnosed after ART initiation as incident KS; in a second sensitivity analysis, we excluded all patients diagnosed with KS within the first 6 months after ART initiation as prevalent KS cases. We also assessed whether time spent on ART (1–6 months versus >6 months after ART initiation) affected the risk factors for developing KS. Interaction was assessed using likelihood ratio tests. Results are presented as medians with interquartile ranges (IQR), incidence rates per 100,000 pys, Kaplan–Meier estimates of the cumulative incidence rate of KS, and crude and adjusted hazard ratios (HR) with 95% confidence intervals (95% CIs). All analyses were performed in MySQL (Community Server, GPL, version 5.5.11) and R (version 2.13.1; The R Foundation for Statistical Computing).

RESULTS

Characteristics of Cohorts and Patients

Of 22 cohorts in the IeDEA-SA database, 16 cohorts with 141,423 patients did not systematically record KS episodes and were therefore excluded from the analysis. Another 19,519 patients were excluded for reasons detailed in Figure S1 (see **Supplemental Digital Content,** http://links.lww.com/QAI/A572).

We included data from 173,245 patients (52%) with 564 incident KS cases drawn from 6 cohorts located in 4 countries (Botswana, South Africa, Zambia, and Zimbabwe). Eighty-seven percent of patients (150,732) were drawn from the Centre for Infectious Disease Research in Zambia (CIDRZ) cohort. The median age at ART initiation was 34 years (IQR: 28–41), and most patients were female (105,787; 61%). Median CD4 cell count at ART initiation was 142 cells per microliter (IQR: 72–218).

Those we excluded had similar proportions of women and girls (60% versus 61%) and a similar age distribution (median age: both 34 years) as those we included but were more likely to be in WHO clinical stage IV at ART initiation (29% versus 9%). We excluded a total of 2684 KS cases from our analysis; 2521 (94%) because they were prevalent cases.

Overall, 564 patients developed KS and 172,681 patients did not. Median age at ART initiation was similar in patients who did and did not develop KS (median age: 35 versus 34 years). Patients with KS had lower median CD4 cell counts at ART initiation than patients who did not develop KS (126 versus 142 cells/μL). Median follow-up time for all included patients was 582 days (IQR: 241–1115 days). In individuals who developed incident KS, median time from ART initiation to diagnosis with KS was 229 days (IQR: 74–550 days). In patients aged ≥5 years, CD4 cell counts at ART initiation were missing for 24,269 individuals (15%) who did not develop KS and 105 individuals (19%) who developed KS. Patients with missing CD4 cell counts at ART initiation were slightly more likely to be in WHO clinical stage III/IV at ART start than patients for whom CD4 cell counts at ART start were available (69% versus 60%).

Incidence Rates and Risk Factors for Developing KS

Table 1 shows the number of KS cases, person-years under observation, and incidence rates. Overall, the incidence rate for KS in patients on ART was 164/100,000 pys (95% CI: 151 to 178). The KS incidence rate was 413/100,000 pys (95% CI: 342 to 497) 30–90 days after ART start, decreased to 188/100,000 pys (95% CI: 157 to 225) 6–12 months after ART initiation, and reached 86/100,000 pys (95% CI: 71 to 105) >2 years after ART start (Fig. 1). After 5 years on ART, the cumulative incidence of KS was 0.5% (95% CI: 0.43 to 0.58) in women and 0.71% (95% CI: 0.62 to 0.83) in men. KS incidence rate was lower in Zimbabwe than in Botswana, South Africa, and Zambia. However, CIs overlapped widely. KS incidence rate increased steeply with age in children and young adults, reached a plateau around age 30, and increased after age 60 (Fig. 2). KS incidence rate was 59/100,000 pys in HIV-infected children and adolescents (aged <16 years) and 173/100,000 pys in HIV-infected adults (aged ≥16 years).

In univariable analyses, the risk for developing KS increased with age and with decreasing current CD4 cell counts (Table 1). Men were more likely than women to develop KS. Patients starting ART in WHO clinical stage III/IV did not have a higher risk for developing KS than patients starting ART in WHO clinical stage I/II. A sensitivity analysis showed that patients who started ART at WHO stage IV were significantly more likely to develop KS than patients starting ART at earlier WHO stages [HR: 2.48; 95% CI: 2.00 to 3.08]. We found no evidence for an association between current or past TB and the risk for developing KS (data not shown). CD4 cell counts at ART initiation were not clearly associated with the risk for developing KS. In patients who started ART at CD4 cell counts <350 cells per microliter, the risk for developing KS decreased with increasing CD4 cell counts at ART initiation (200–349 versus <50 cells/μL; HR: 0.64; 95% CI: 0.47 to 0.87). In contrast, in patients with CD4 cell counts ≥350 cells per microliter at ART initiation, KS risk was higher than in patients with CD4 cell counts <50 cells per microliter at ART initiation (HR: 1.28; 95% CI: 0.86 to 1.89). This finding was confirmed when we included prevalent KS cases and also when we excluded all persons diagnosed with KS within the first 6 months after ART initiation for the purpose of sensitivity analyses.

In multivariable analyses adjusted for age, sex, current CD4 cell counts, WHO clinical stage at ART initiation, and the calendar year, we confirmed adulthood, male sex, and low current CD4 cell counts as independent risk factors for developing KS (Table 2). In patients with current CD4 cell counts ≥500 cells per microliter, the risk for developing KS was reduced by 64% compared with patients with current CD4 cell counts <50 cells per microliter (HR: 0.36; 95% CI: 0.23 to 0.55). KS incidence rate increased with the calendar year of ART initiation. Patients who started ART between 2007 and 2010 were more likely to be diagnosed with KS than patients who started ART between 2004 and 2006 (adjusted HR: 1.50; 95% CI: 1.23 to 1.83). This finding was not explained by more severe immunosuppression in patients who started ART between 2007 and 2010. In contrast, patients who started ART in earlier years had a lower median CD4 cell count at ART initiation than patients who started between 2007 and 2010: 117 cells per microliter (IQR: 55–188) versus 154 cells per microliter (IQR: 81–232). Patients who started ART in earlier years were also more likely to present with WHO clinical stage IV than patients who started between 2007 and 2010 (13% versus 7%). WHO stage at ART initiation was the only risk factor that showed a significant interaction with time on ART (1–6 months versus >6 months after ART initiation). In the multivariable analysis, the overall HR for WHO stage III/IV versus I/II at ART initiation was 1.10, not reaching conventional levels of statistical significance. However, during the first 6 months of treatment, the adjusted HR was 1.52 (95% CI: 1.11 to 2.08) and 0.90 (95% CI: 0.71 to 1.14) thereafter; *P*-value for interaction was 0.023.

DISCUSSION

The incidence rate of KS in HIV-infected patients treated with ART remains high (164/100,000 pys). KS incidence rate was 413/100,000 pys 30–90 days after ART initiation and decreased to 86/100,000 pys >2 years after ART initiation. Low current CD4 cell counts increased the risk for developing KS. Adults were more likely to develop KS than children, and men were more likely to develop KS than women.

This is one of the first reports to describe KS incidence rates in patients on ART in an African setting, and it is, to our knowledge, the first study to report KS incidence rates in HIV-infected African children on ART. We included more than 170,000 children and adults from 4 Southern African countries. The multicohort design of the study allowed us to evaluate prospectively collected information on KS cases and patient visits. Opportunistic infections and CD4 cell counts were reported regularly. CD4 cell count measurements at ART initiation were available for 85% of included patients, and WHO stages at ART start were recorded for 96% of the included participants.

However, our study was limited because we included only 6 of the 22 cohorts that participate in IeDEA-SA, and 87% of patients we included were drawn from the CIDRZ cohort in Zambia. Our findings are, therefore, mainly

TABLE 1. KS Incidence Rates and Unadjusted Hazard Ratios for Developing KS in Patients on ART

	Patients (N)	Person-Years at Risk	KS Cases (N)	Incidence Rate per 100,000 pys (95% CI)	HR (95% CI)
All	173,245	343,927	564	164 (151 to 178)	—
Country					
Botswana	704	1490	2	134 (34 to 537)	—
South Africa	19,532	34,717	48	138 (104 to 183)	—
Zambia	150,732	302,543	510	169 (155 to 184)	—
Zimbabwe	2277	5177	4	77 (29 to 206)	—
Sex					
Female	105,787	213,306	296	139 (124 to 156)	1.00
Male	67,457	130,616	268	205 (182 to 231)	1.45 (1.23 to 1.72)
Age at ART start (yrs)					
<5	6290	11,329	3	26 (9 to 82)	0.15 (0.05 to 0.45)
5–9	3758	8712	3	34 (11 to 107)	0.20 (0.06 to 0.62)
10–15	3201	7099	10	141 (76 to 262)	0.80 (0.43 to 1.51)
16–29	41,591	76,325	114	149 (124 to 179)	0.80 (0.64 to 0.99)
30–39	70,454	141,599	257	181 (161 to 205)	1.00
40–49	34,174	71,570	130	182 (153 to 216)	1.01 (0.82 to 1.25)
50–59	10,758	21,941	33	150 (107 to 212)	0.83 (0.58 to 1.19)
≥60	3017	5349	14	262 (155 to 442)	1.37 (0.80 to 2.34)
Calendar year at ART start					
2004–2006	54,717	177,507	192	108 (94 to 125)	1.00
2007–2010	118,528	166,420	372	224 (202 to 247)	1.49 (1.24 to 1.79)
WHO stage at ART start					
I-II	64,121	117,855	182	154 (134 to 179)	1.00
III-IV	102,301	213,594	367	172 (155 to 190)	1.16 (0.97 to 1.39)
Missing	6823	12,477	15	120 (72 to 199)	—
CD4 at ART start (cells/μL)*					
<50	25,060	49,981	92	184 (150 to 226)	1.00
50–99	26,229	54,076	96	178 (145 to 217)	0.94 (0.71 to 1.26)
100–199	51,479	104,069	156	150 (128 to 175)	0.78 (0.60 to 1.01)
200–349	32,485	58,217	77	132 (106 to 165)	0.64 (0.47 to 0.87)
350–499	4511	8439	21	249 (162 to 382)	1.23 (0.76 to 1.98)
≥500	2815	5046	14	277 (164 to 468)	1.36 (0.77 to 2.38)
Missing	24,374	52,767	105	199 (164 to 241)	—
Current CD4 (cells/μL)*					
<50	—	16,636	67	403 (317 to 512)	1.00
50–99	—	21,629	66	305 (240 to 388)	0.81 (0.57 to 1.14)
100–199	—	62,296	136	218 (185 to 258)	0.65 (0.48 to 0.87)
200–349	—	94,036	128	136 (114 to 162)	0.49 (0.36 to 0.67)
350–499	—	59,652	75	126 (100 to 158)	0.54 (0.38 to 0.77)
≥500	—	55,727	37	66 (48 to 92)	0.31 (0.20 to 0.47)
Missing	—	22,619	52	230 (175 to 302)	—

*Children aged <5 years were excluded from analyses of absolute CD4 cell counts.

representative for Zambia, and to a lesser extent for Southern Africa as a region. Only cohorts in South Africa and Botswana collect HIV viral loads routinely. Therefore, we could not include HIV viral loads in our models. Because HHV-8 serology is generally not available, we could not assess the risk for developing KS among coinfected patients. In addition, KS is often only clinically diagnosed and not histologically confirmed. This might have led to misclassification of KS cases and consecutively an underestimation or overestimation of the KS incidence rate in our cohorts.

The incidence rate we estimated (in adult patients 173/100,000 pys) is not far from incidence rates observed in adult HIV-infected patients on ART in Uganda (201/100,000 pys), Kenya (270/100,000 pys),[8] and Switzerland (130/100,000 pys)[11] (Table 3). Fink et al[20] reported a substantially higher KS incidence rate (450/100,000 pys [95% CI: 320 to 620]) in patients on ART in Central and South America, which might be explained by different definitions of incident KS cases. Fink et al included all KS cases that were diagnosed after ART initiation, whereas we excluded KS cases that were diagnosed within the

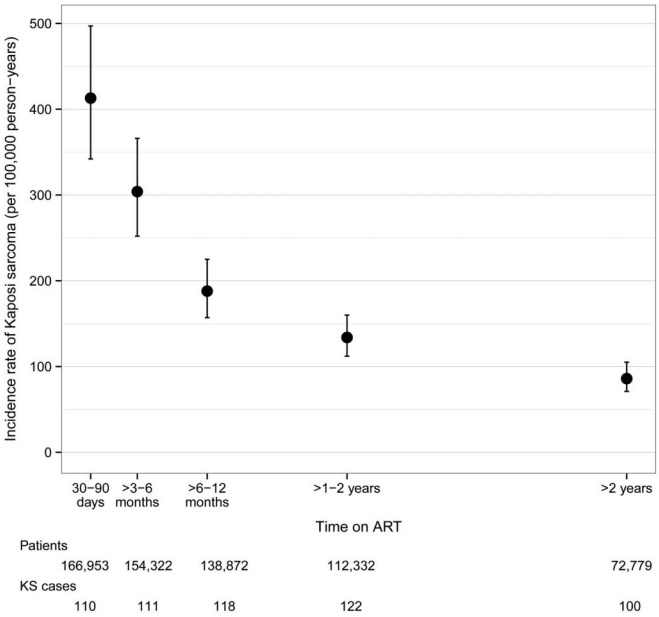

FIGURE 1. KS incidence rates by time on ART.

first month on ART as prevalent cases. Including all KS cases diagnosed after ART initiation as incident cases does not take into account potential delays in KS case ascertainment. A KS case diagnosed a few days after ART initiation might not be a true incident case but rather a prevalent KS case, which was diagnosed with a lag time. It has been shown that the KS incidence estimates decrease as the lag time accounted for increases.[14] However, to date, no standard definition of incident KS exists and cutoffs are chosen arbitrarily with lag times commonly ranging between 0 and 90 days.[8,11,13]

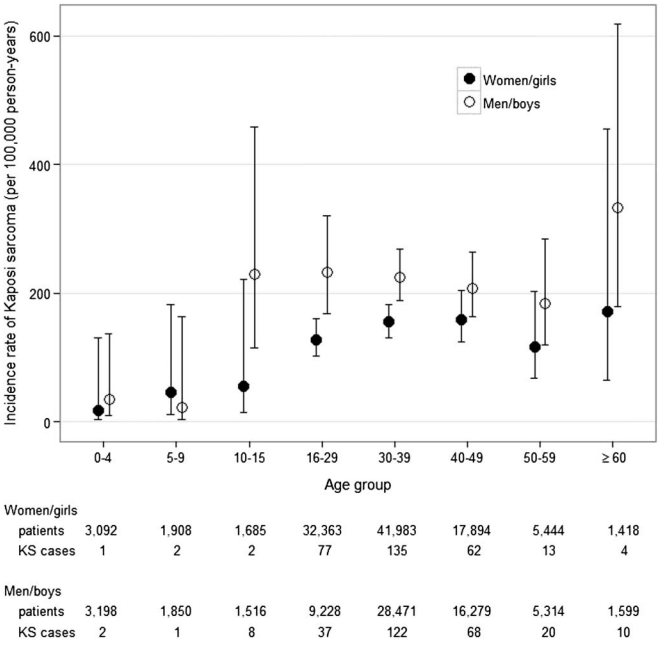

FIGURE 2. KS incidence rates by age groups, stratified for gender.

TABLE 2. Risk Factors for Developing KS in Patients on ART

	Adjusted Hazard Ratio (95% CI)*
Sex	
Female	1.00
Male	1.34 (1.12 to 1.61)
Age at ART start (yrs)	
5–9	0.20 (0.05 to 0.79)
10–15	0.74 (0.35 to 1.57)
16–29	0.87 (0.68 to 1.10)
30–39	1.00
40–49	1.02 (0.81 to 1.27)
50–59	0.85 (0.58 to 1.24)
≥60	1.42 (0.81 to 2.49)
Calendar period at ART start	
2004–2006	1.00
2007–2010	1.50 (1.23 to 1.83)
WHO stage at ART start	
I–II	1.00
III–IV	1.10 (0.91 to 1.32)
Current CD4 (cells/μL)	
<50	1.00
50–99	0.82 (0.58 to 1.16)
100–199	0.65 (0.48 to 0.88)
200–349	0.52 (0.38 to 0.71)
350–499	0.59 (0.41 to 0.84)
≥500	0.36 (0.23 to 0.55)

*Adjusted for all variables listed, that is, sex, age, calendar period, WHO stage, and current CD4 cell count. Children aged <5 years were excluded from this analysis.

In this study, as in other studies, KS incidence rate was highest within the first 6 months after ART initiation and declined steeply thereafter.[16,19] The high KS incidence rate observed within the first 6 months on ART might partly be explained not only by prevalent cases that have been misclassified as incident cases but also by unmasking immune reconstitution inflammatory syndrome.[21] Once HIV-infected patients have been on ART for more than 2 years, KS incidence was relatively low (86/100,000 pys). Of note, this relatively low incidence rate is still higher than the age standardized incidence rates of the most common cancers in the general populations of Zambia, Zimbabwe, South Africa, and Botswana combined, as estimated by GLOBOCAN 2012 (prostate cancer: 56.3/100,000 pys, cervical cancer: 37.6/100,000 pys).[22]

Interestingly, we found that KS incidence rates increased with the calendar year. We could not find a biological explanation for this unexpected trend and hypothesize that it is caused by more accurate and intensive diagnosing and reporting in more recent years. Estimated KS incidence rates in Zambia, Botswana, and South Africa were similar, whereas the incidence rate in Zimbabwe was lower. The lower incidence rate could reflect the lower HHV-8 seroprevalence of 35% reported in HIV-infected persons in Zimbabwe as compared with 50% HHV-8 seroprevalence in Zambia and South Africa.[1,2] It could also be due to differences in KS diagnosing and recording between the included cohorts. However, the difference in the KS incidence rates

TABLE 3. KS Incidence Rates in Patients on ART in Resource-Rich and Resource-Limited Regions

Authors	Cohort	Country	Calendar Years	Patients on ART	KS Incidence Rate per 100, 000 pys	
Resource-rich regions				N	Children	Adults
Ledergerber et al[12]	SHCS	Switzerland	1995–1999	2410	NR	140
Clifford et al[13]	SHCS	Switzerland	1985–2003	NR	NR	109
Franceschi et al[11]	SHCS	Switzerland	1984–2006	NR	NR	130
Suarez-Garcia et al[14]	CoRIS/CoRIS-MD	Spain	1997–2008	NR	NR	199
Carrieri et al[15]	DMI-2	France	1996–2001	2589	NR	122
Lacombe et al[16]	FHDH-ANRS CO4	France, French overseas territories	1992–2009	40,083	NR	137
Mocroft et al[17]	EuroSIDA	Europe, Israel	1994–1999	NR	NR	700
Lodi et al[18],*	CASCADE	Europe, Australia, Canada	1986–2006	4199	NR	358
Yanik et al[19]	CNICS	United States	1996–2011	11,485	NR	304
Resource-limited regions						
Fink et al[20]	CCASAnet/IeDEA	Caribbean, Central and South America	2007–2009	3372	NR	450
Asiimwe et al[9]	HBAC	Uganda	2003–2008	1121	NR	340
Martin et al[8]	IeDEA	Uganda	2008–2011	NR	NR	201
Martin et al[8]	IeDEA	Kenya	2008–2011	NR	NR	270
Current study	IeDEA	Southern Africa	2004–2010	173,245	59	173

Estimates from different studies are adjusted for different variables.

*Includes only men who have sex with men.

CASCADE, Concerted Action of Seroconversion to AIDS and Death in Europe; CCASAnet, Caribbean, Central and South American network for HIV research; CNICS, Centers for AIDS Research (CFAR) network of integrated clinical systems; CoRIS/CoRIS-MD, Spanish cohorts of naive HIV-infected patients; DMI-2, longitudinal database of HIV-infected individuals followed at Nice University Hospital, France; EuroSIDA, collection of European cohort studies; FHDH-ANRS CO4, The French Hospital Database on HIV; HBAC, Home-Based AIDS Care program; SHCS, Swiss HIV Cohort Study; NR, not reported.

between Zimbabwe and the other countries was not statistically significant. We found that KS incidence rates increased from childhood to adulthood and plateaued around age 30. After age 60, KS incidence rate increased again, but this increase was not statistically significant and could be a spurious finding. An increase of KS incidence rate in older adults would be in line with a previous study[23] and could be explained by aging, which is a risk factor for developing cancer in general and acquiring HHV-8 infection in particular; population-based studies from Africa have shown that HHV-8 seroprevalence increases with age.[24–26] The same trend was described in HIV-infected persons in Ghana.[27] Men were at higher risk for developing KS than women, although we found no difference in the KS incidence rate between boys and girls. Most studies in Africa found HHV-8 seroprevalence to be only slightly higher in men than women.[28–30] Other mechanisms such as direct and indirect effects of sex hormones[31] and sex differences in immune response to HHV-8 infection might play a role in KS development. We found no evidence for an association between TB and KS, which is in line with a previous study.[32] Advanced WHO clinical stage was a risk factor for developing KS in the first 6 months after ART initiation but not thereafter. This finding might be explained by survival bias of those on ART for more than 6 months.

Unlike other studies,[9,19] we found no clear association between CD4 cell counts at ART initiation and KS incidence rate. In patients with CD4 cell counts <350 cells per microliter at ART start, KS risk decreased as CD4 cell counts at ART start increased. Surprisingly, patients who started ART at CD4 cell counts ≥350 cells per microliter had a higher risk for developing KS than patients who started ART at CD4 cell counts <50 cells per microliter. However, this finding may result from selection bias. At the time of this study, patients were eligible for ART if they presented at WHO stage IV or with CD4 cell counts <200 or 350 cells per microliter (depending on the cohort and calendar year). Patients who started ART at CD4 counts ≥350 cells per microliter must have had AIDS symptoms to qualify for ART. The condition that made these patients eligible for ART might also have increased their risk for developing KS. Likewise, patients with CD4 cell counts <50 cells per microliter might have already developed KS at baseline, and thus might have been excluded as prevalent cases. However, even when we included all prevalent KS cases in a sensitivity analysis, the observed pattern for the association between CD4 cell counts at ART start and KS incidence rates remained similar. Missing CD4 cell counts at ART start might have also introduced a selection bias. Very sick patients in advanced WHO clinical stages are more likely to start ART without a CD4 cell count measurement than patients with early stage disease. This was also the case for our sample: patients with missing CD4 cell counts at ART initiation were more likely to be in WHO clinical stages III/IV than patients with available CD4 cell counts (69% versus 60%). Finally, current CD4 cell counts, which might be less affected by selection biases, showed a clear decline in KS risk as CD4 cells counts increased. This finding is consistent with those of previous studies conducted in high-income[18,23] and

low-income settings.[8] Because maintaining CD4 cell counts ≥500 cells per microliter decreases the risk for developing KS, it seems likely that starting ART at CD4 cell counts <500 cells per microliter—as recently recommended by the WHO[33]—could further reduce the incident KS burden.

Despite ART, the incidence rate of KS in HIV-infected patients remains high and is especially high within the first 6 months after ART initiation. The KS burden might be further reduced by early HIV testing and maintaining high CD4 cell counts.

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